TITLE: Extracorporeal Membrane Oxygenation for Cardiac Failure: A Review of the Clinical Effectiveness and Guidelines

DATE: 11 December 2014

CONTEXT AND POLICY ISSUES

Heart failure is a condition in which abnormality in cardiac structure or function results in an inability of the heart to fill or eject blood at a rate commensurate with the body's requirements.[1,2] Heart failure is also referred to as cardiac failure and the terms are often used interchangeably. There are two major types of heart failure: diastolic heart failure which is associated with abnormal heart filling and systolic heart failure which is associated with abnormal heart emptying.[3] Manifestation of heart failure include shortness of breath, fatigue, and fluid retention.[4] Heart failure may be caused by disorders of the pericardium, myocardium, endocardiam, heart valves or great vessels, or certain metabolic abnormalities.[2] It is estimated that in Canada there are 500,000 patients living with heart failure and 50,000 new patients are diagnosed every year.[5] The prognosis for heart failure patients is poor, with an average 1-year mortality rate of 33%.[6]

Several mechanical circulatory support devices are used for patients with heart failure. Included among these are extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD). ECMO is also referred to as extracorporeal life support (ECLS). VAD comprises a mechanical pump which is used to support blood flow and heart function in the case of weakened hearts.[7] There are two main types of VAD: left ventricular assist device (LVAD) and right ventricular assist device (RVAD). When both types are used together it is called a biventricular assist device (BiVAD).[7] The ECMO system consists of an oxygenator and a pump and allows blood to be drained from the native vascular system, circulated outside of the body and then returned into the circulation via a an arterial or venous route.[8-10] During ECMO, oxygen is added and carbon dioxide is removed from the blood.[8] There are primarily two types of ECMO depending on the route of access: venovenous ECMO (VV ECMO) and arterialvenous ECMO (VA ECMO). ECMO is a complex procedure and requires a multidisciplinary team. It is an invasive procedure with inherent complications associated with it. Complications associated with ECMO use include bleeding, pneumonia or sepsis, and renal failure.[11,12]

The purpose of this report is to review the available evidence on clinical effectiveness of ECMO compared to other modalities for heart failure patients and in addition to review the evidence-based guidelines on use of ECMO for heart failure patients.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of extracorporeal membrane oxygenation for patients with cardiac failure?

2. What is the comparative effectiveness of extracorporeal membrane oxygenation compared with a percutaneous ventricular assist device for patients with severe cardiac failure?

3. What are the evidence-based guidelines regarding the use of extracorporeal membrane oxygenation for patients with cardiac failure?

KEY FINDINGS

No data comparing ECMO with conventional cardiopulmonary resuscitation (C-CPR) specific to heart failure patients were available. Limited evidence from a mixed population with a proportion of heart failure patients suggests better survival with ECMO compared with C-CPR, however results were not always statistically significant.

Results of comparisons of ECMO with VAD were few and inconsistent and definite conclusions are not possible.

One evidence-based guidance document, recommended that for adults with acute heart failure undergoing ECMO, the procedure should be undertaken by clinical teams with specific training and expertise in the procedure.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1990 and November 14, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients in the ICU with cardiac failure
Intervention	Extracorporeal membrane oxygenation (may also be called extracorporeal life support)
Comparator	Any
Outcomes	Clinical effectiveness (recovery, survival, bridge to other therapy, quality of life) Safety Evidence-based guidelines (including conduct of ECMO and patient management [including initiation, weaning, ventilation and anticoagulation], personnel required, contraindications/prioritization, and quality assurance)
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT). Non-randomized studies to be included only if few HTA/SR/MA/RCTs available

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 1990. Non-comparative studies such as case series and case reports were excluded as these studies are generally considered to be of low quality and observed outcomes are difficult to attribute to the intervention being used. Studies on neonates were excluded. Individual studies that were already included in an included systematic review were excluded. Studies that did not mention heart failure or cardiac failure patients in the patient population studied were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[13] was used for systematic reviews; the Downs and Black checklist[14] for RCTs and non-randomized studies.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 650 citations were identified in the literature search. Following screening of titles and abstracts, 598 citations were excluded and 52 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 46 publications were excluded for various reasons, while seven publications met the inclusion criteria and were included in this report. These seven publications comprised of one systematic review,[15] four non-randomized studies,[16-20] and one guidance document.[21] Of the seven publications, two publications[16,17] were

based on one study and both were included as each reported some unique data. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included systematic review and non-randomized studies are summarized below and details are provided in Appendix 2

ECMO versus other modalities but excluding VAD

Three relevant non-randomized studies[17-19] comparing ECMO with conventional cardiopulmonary resuscitation (C-CPR) in an adult population which included a portion of heart failure patients were identified (C-CPR). Specific details on the intervention and severity of disease were not provided. Two studies[18,19] were prospective and one study[17] was retrospective. The studies were from Korea and Japan and published between 2008 and 2013. The total number of patients varied between 54 and 102 and the mean age varied between 55 and 60 years.

ECMO versus VAD

One systematic review[15] and one prospective non-randomized study[20] comparing ECMO with VAD were identified. The systematic review included three relevant non-randomized studies on patients with heart transplant failure. It was published in 2013 from the Czech Republic. The total number of patients in the three included studies was 143. Patient age was not reported. The non-randomized study included pediatric patients with severe heart failure undergoing bridge to heart transplant. It was published in 2012 from USA. The total number of patients was 144 and was divided into two cohorts (Cohort 1 and 2) by body surface area (BA) Each cohort had 96 patients. Median age in the cohorts 1 and 2 were 10.6 months and 138.7 months, respectively, for the ECMO group and 11.7 months and 111.2 months in the VAD (Berlin Heart) group. The VAD group received either LVAD and BiVAD

ECMO guidelines

One evidence-based guidance document[21] on general recommendations for ECMO was identified. It was published from the United Kingdom (UK) in 2014. It is an interventional procedure guidance prepared by the National Institute for Health and Care Excellence (NICE)

Summary of Critical Appraisal

Strengths and limitations of individual studies are provided in Appendix 3.

ECMO versus other modalities but excluding VAD

Three relevant non-randomized studies[17-19] were identified. Two were prospective studies[18,19] and one was a retrospective study.[17] In all three studies the objectives and inclusion criteria were clearly stated; patient characteristics, interventions and outcomes were described, and propensity score matching of groups was conducted. Hidden bias may remain despite propensity score matching due to unmeasured covariates. Initiation of ECMO was the decision

of the attending physician hence potential for bias in patient selection. Generalizability is limited as these were single centre studies.

ECMO versus VAD

One systematic review[15] and one prospective non-randomized study[20] were identified for inclusion.

In the systematic review, the objective was clearly stated and the list of included studies was provided. A single database was searched and provided a literature search strategy. Characteristics of the individual studies were provided but lacked detail. Inclusion and exclusion criteria were not explicitly stated. Article selection and data extraction were not described. Assessments of quality of the studies or publication bias appear not to have been conducted.

In the non-randomized study the objective, and inclusion and exclusion criteria were clearly stated; patient characteristics, interventions and outcomes were described; and propensity score matching of groups was conducted. As with the other non-randomized studies, hidden bias may remain despite propensity score matching due to unmeasured covariates. The ECMO group was the control group in this study and it was a historical control. The historical control patients were taken from the Extracorporeal Life Support Organization (ELSO) registry for ECMO support during 2000 to 2007 and this VAD study was published in 2012. As ECMO technology has evolved over the years, this may not be a fair comparison. This study was partly funded by the manufacturer of the VAD.

ECMO guidelines

One evidence-based guidance document[21] was identified. It was a brief document and did not contain enough information to conduct a critical appraisal. However the guidance document was prepared using processes described in the NICE Interventional Procedures Programme methods guide.[22] These processes include identification, selection, and collation of appropriate evidence; assessment of evidence and consideration of the evidence and commentary (including specialist advice and lay input) by a committee. The committee in making the recommendations for ECMO considered evidence of efficacy and safety from published literature and specialist advice.

Summary of Findings

The overall findings from the systematic review and non-randomized studies are summarized below and details are available in Appendix 4.

What is the clinical effectiveness of extracorporeal membrane oxygenation for patients with cardiac failure?

In two studies,[17,18] the in-hospital survival was higher in the ECMO group compared to the conventional group (31.7% versus 10.0% [P = 0.01] and 29.6% versus 18.5% [P = NR]). Also in these two studies, the 6-month survival was numerically better in the ECMO group compared to the conventional group (26.7% versus 8.3% [P = 0.02] and 29.6% versus 14.8% [P = 0.33]). However, the differences were not always statistically significant. The hazard ratios for survival were calculated in all the three studies and are presented in Table 1. Results were statistically

significant in two studies[17,19] and not statistically significant in one study.[18] Survival with minimal neurological impairment (CPC ≤ 2) was numerically higher in the ECMO group compared to the conventional group, though always not statistically significant as shown in Table 2.

Table 2: Summary of outcomes with ECMO versus conventional care

Outcome	Effect		
	Shin,[16,17] 2011	Lin,[18] 2010	Chen,[19] 2008
Survival; HR (95% CI) unless otherwise stated			
In-hospital	0.17 (0.04 to 0.71)[a]	NR	NR
30-day	NR	0.86 (0.45 to 1.62)	0.47 (0.28 to 0.77)
6-month	0.50 (0.30 to 0.84)	0.59 (0.32 to 1.08)	NR
1-year	0.55 (0.37 to 0.83)	0.60 (0.33 to 1.09)	0.53 (0.33 to 0.83)
2-year	0.56 (0.37 to 0.84)	NR	NR
Neurological status (CPC ≤ 2); (%)			
At discharge	26.7 vs 8.8 (P = 0.04)	25.6 vs 18.5 (P = 0.46)	30.4 vs 15.2 (P = 0.09)
At 6-month	26.7 vs 6.7 (P = 0.04)	NR	NR
1-year	NR	18.5 vs 11.1 (P = 0.43)	19.5 vs 10.8 (P = 0.27)

[a]OR (95% CI)

CI: Confidence Interval; CPC: cerebral performance category; HR: Hazard Ratio; NR: Not reported; OR: Odds Ratio

What is the comparative effectiveness of extracorporeal membrane oxygenation compared with a percutaneous ventricular assist device for patients with severe heart failure?

The systematic review[15] including three relevant studies, showed numerically higher survival with ECMO compared to VAD in two studies (54% versus 33% [P = 0.27] and 50% versus 33% [P = NR]) and similar survival in one study. The non-randomized study showed that mortality was higher with ECMO compared to VAD (20.8% versus 4.2% at 30 days and 20.8% versus 8.3% at the end of the circulatory support).

What are the evidence-based guidelines regarding the use of extracorporeal membrane oxygenation for patients with cardiac failure?

One evidence-based guidance document[21] recommended that for adults with acute heart failure undergoing ECMO, the procedure should be undertaken by clinical teams with specific training and expertise in the procedure.

Limitations

There were no studies with matched groups comparing ECMO with C-CPR in patients specifically with heart failure. The studies comparing ECMO with C-CPR included a mixed population in which a certain proportion of patients had heart failure and results were not presented separately for the heart failure patients. Hence results need to be interpreted with caution.

Two studies comparing ECMO with C-CPR were from the same group and patients appear to be recruited over the same time period, hence there may be overlap of patients and the results may not be completely exclusive.

The systematic review comparing ECMO with VAD lacked detail in its reporting.

All included studies were non-randomized studies, and the included systematic review also assessed non-randomized studies, hence there is potential for selection bias. Although propensity score matching was conducted to minimize selection bias, hidden bias may still remain due to unmeasured covariates. Comparative adverse events data were not reported in any of the studies.

Comparison across studies was difficult as there was considerable variation in study population, setting, and conduct of procedures. Due to paucity of data as well as inconsistencies in the results, definitive conclusions are not possible. Generalizability was limited as the studies were mostly conducted at single centres.

Most of the studies were not conducted in a Canada hence results may not be applicable to a Canadian setting. One non-randomized study on pediatric patients comparing VAD with a historical ECMO control included some patients from Canadian centres in the VAD group but the countries of patients in the ECMO group were not mentioned.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No data comparing ECMO with conventional cardiopulmonary resuscitation (C-CPR) specific to heart failure patients were available. Limited evidence from a mixed population with a proportion of heart failure patients, suggests better survival with ECMO compared with C-CPR, however results were not always statistically significant. Results of comparison of ECMO with VAD were few and inconsistent and definite conclusions are not possible. There is a lack of comparative studies but a systematic reviews with studies using data from registries showed that in-hospital mortality was 54% (95% CI: 47% to 61%) in adult cardiac patients receiving ECMO.[23]

One evidence-based guidance document, recommended that for adults with acute heart failure undergoing ECMO, the procedure should be undertaken by clinical teams with specific training and expertise in the procedure. Guidelines on conduct of ECMO, contraindications, personnel requirements and patient management were not available

A registry of ECMO use is being maintained by the Extracorporeal Life Support Organization (ELSO). It is an international consortium of health care professionals and scientists and is involved in the development and evaluation of novel therapies for support of failing organ systems and its primary mission is to maintain a registry of, at least, use of ECMO in active ELSO centers.[24] The data are used for the purpose of quality assurance and decision making.[25] Registry data showed that with the use of ECMO, the survival to discharge or transfer, were respectively 41% and 29% in pediatric and adult patients with cardiopulmonary conditions and 50% and 40% for pediatric and adult patients with cardiac conditions.[26]

ECMO is an invasive procedure and as such is associated with inherent adverse events. It is a complex procedure and guidelines recommend a multidisciplinary team with appropriate training and expertise.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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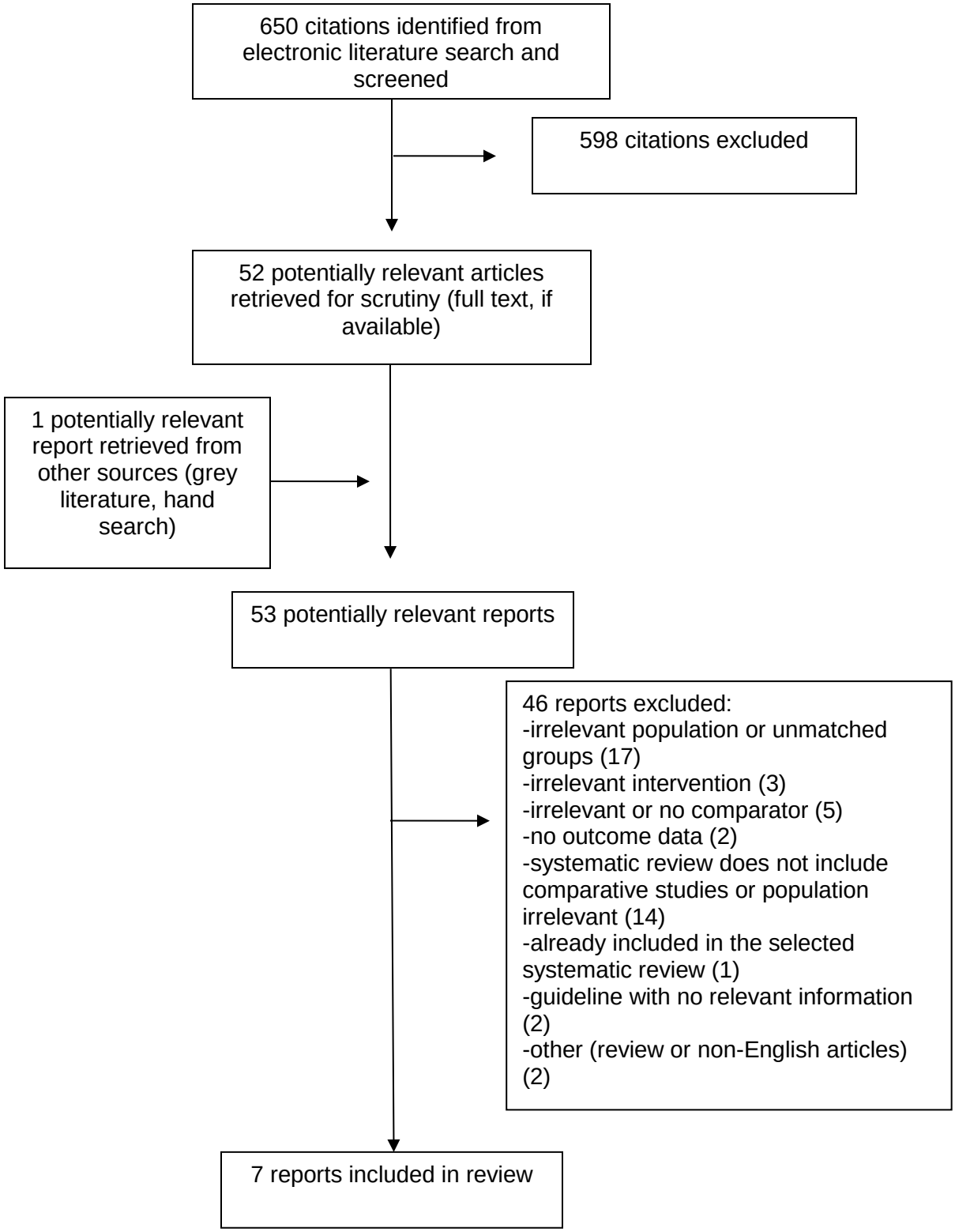
ABBREVIATIONS

BA	body surface area
BiVAD	biventricular assist device
C-CPR	conventional cardiopulmonary resuscitation
CI	confidence interval
CPC	cerebral performance category
CPR	cardiopulmonary resuscitation
ECMO	extracorporeal membrane oxygenation
E-CPR	extracorporeal cardiopulmonary resuscitation
ELSO	extracorporeal life support organization
HR	hazard ratio
LOS	length of stay
LVAD	left ventricular assist device
NA	not available
NR	not reported
OR	odds ratio
RVAD	right ventricular assist device
VAD	ventricular assist device

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Outcomes Measured
ECMO versus other (excluding VAD)				
Non-randomized studies (NRS)				
Shin,[17] 2011, Korea	NRS, retrospective. Propensity score matched groups. Tertiary care university hospital l (January 2003 to June 2009)	Adult patients with in hospital cardiac arrest (including heart failure: 16.7% in E-CPR and 20.0% in C-CPR in matched groups) N = 120 (60 ECMO, 60 C-CPR; matched) Age (years) (mean ± SD): 60.8 ± 14.5 in E-CPR and 60.5 ± 15.5 in C-CPR. % Male: 60.0 in E-CPR and 68.3 C-CPR	E-CPR (ECMO) vs C-CPR	Survival
Lin,[18] 2010, Taiwan	NRS, prospective. Propensity score matched groups. University affiliated medical centre (National Taiwan University Hospital). (2004 to 2006)	Adult patients with in hospital cardiac arrest of cardiac origin (including heart failure: 7.3% in E-CPR and 14.3% in C-CPR in total group of 118, % not reported for matched group of 54). N = 54 (27 in E-CPR and 27 in C-CPR) Age (years) (mean ± SD): 59 ± 11 in E-CPR and 60.6 ± 12.7 in C-CPR %Male: 77.8 in E-	E-CPR (ECMO) vs C-CPR	Survival

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Outcomes Measured
		CPR and 85.2 in C-CPR		
Chen,[19] 2008, Taiwan	NRS prospective. Propensity score matched groups. University affiliated medical centre. (National Taiwan University Hospital). (January 2004 to December 2006)	Adult patients with in hospital cardiac arrest of cardiac origin (including heart failure: 10.9% in E-CPR and 19.6% in C-CPR in matched group N = 92 (46 in E-CPR and 46 in C-CPR) Age (years) (mean ± SD): 57 ± 14 in E-CPR and 55 ± 15 in C-CPR %Male: 85 in E-CPR and 87 in C-CPR	E-CPR (ECMO) vs C-CPR	Survival
ECMO versus VAD				
HTA/SR				
Urban,[15] 2013, Czech Republic	SR included 8 studies (3 comparative and 5 single arm studies). The 3 comparative studies that are relevant for our review are presented here.	Heart transplanted patients with acute graft failure. N = 143 Age = NR % Male = NR	ECMO versus VAD (RVAD or BiVAD)	Survival
Non randomized study				
Fraser,[20] 2012, USA	NRS, prospective. Multi centre (in USA and Canada), single arm (VAD) study comprising of two cohorts according to BA. Each cohort then compared with	Pediatric patients with severe heart failure with bridge to heart transplant. N = 144 Cohort 1: (BA< 0.7 m^2): 24 VAD & 48	ECMO (matched historical control) versus VAD	Survival, Weaning

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Outcomes Measured
	propensity score matched historical ECMO cohort (from ELSO registry).	ECMO Cohort 2: (BA 0.7 to <1.5 m^2): 24 VAD & 48 ECMO Age (month) (median [range]): <u>Cohort 1</u> 10.6 [0.1 to 112.3] in ECMO and 11.7 [2.6 to 45.6 in VAD. <u>Cohort 2</u> 138.7 [1.8 to 188.6] in ECMO and 111.2 [50.8 to 191.8] in VAD % Male: <u>Cohort 1</u> NR in ECMO And 50 in VAD <u>Cohort 2</u> NR in ECMO and 54 in VAD		

C-CPR = conventional cardiopulmonary resuscitation; CI = confidence interval; CPC = cerebral performance category; ECMO = extracorporeal membrane oxygenation; E-CPR = extracorporeal cardiopulmonary resuscitation; ELSO = extracorporeal life support organization; NR = not reported; VAD = ventricular assist device

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
ECMO versus other (excluding VAD)		
Non-randomized studies (NRS)		
Shin,[16,17] 2011, 2013, Korea	• Objective was clearly stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Groups matched by propensity score • P-values or 95% CI provided • Authors declared there was no potential conflict of interest	• Non randomized, retrospective, hence subject to bias. • Though propensity score matched analysis was undertaken there is a possibility of unmeasured covariates not considered in the analysis could impact outcome. • Initiation of ECMO was based on the decision of the attending physician, hence potential of bias. • Sample size calculation not described • Generalizability limited as results pertain to a tertiary academic hospital in Korea
Lin,[18] 2010, Taiwan	• Objective was clearly stated. • Inclusion criteria were stated, exclusion criteria were not explicitly stated. • Patient characteristics, interventions, and outcomes were described. • Groups matched by propensity score • Sample size calculation mentioned • P-values or 95% CI provided • Authors mentioned that they had no conflict of interest to declare	• Non randomized hence subject to bias. • Though propensity score matched analysis was undertaken there is a possibility of unmeasured covariates not considered in the analysis could impact outcome. • Initiation of ECMO was based on the decision of the attending physician hence potential for bias. • Generalizability limited as results pertain to a university affiliated medical centre in Taiwan
Chen,[19] 2008, Taiwan	• Objective was clearly stated. • Inclusion/ exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Groups matched by propensity score • P-values or 95% CI provided • Authors declared there was no potential conflict of interest	• Non randomized hence subject to bias. • Though propensity score matched analysis was undertaken there is a possibility of unmeasured covariates not considered in the analysis could impact outcome. • Initiation of ECMO was based on the decision of the attending physician hence potential for bias. • Generalizability limited as results pertain to a university affiliated medical centre in Taiwan

First Author, Publication Year, Country	Strengths	Limitations
ECMO versus VAD		
Systematic review		
Urban,[15] 2013, Czech Republic	• The objective was clearly stated. • Single database (Medline,1996 to August,2012) searched. • List of included studies provided • Characteristics of the individual studies were provided but lacked details • Conflict of interest: none declared	• The inclusion and exclusion criteria were not explicitly stated. • Details of study selection were not described nor was a flow chart presented • List of excluded studies was not provided • Article selection and data extraction details were not provided. • No mention of quality assessments of studies • No mention of exploration of publication bias
Non-randomized study (NRS)		
Fraser,[20] 2012, USA	• Objective was clearly stated. • Inclusion criteria and exclusion criteria were stated. • Patient characteristics, interventions, and outcomes were described. • Groups matched by propensity score • Sample size calculation mentioned • P-values provided • Authors disclosed their conflict of interest.	• Non randomized hence subject to bias. • Though propensity score matched analysis was undertaken there is a possibility of unmeasured covariates not considered in the analysis could impact outcome. Despite propensity score matching, it is possible that in some respects patients in the ECMO group were more ill than those in the VAD group. • ECMO was the control group in this study and was a historical control • This study was partly funded by the manufacturer of VAD

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">ECMO versus other (excluding VAD)</td></tr>
<tr><td colspan="2">Non-randomized studies</td></tr>
<tr><td>Shin,[16,17] 2011, 2013
Korea</td><td>
Main Findings:
Survival with E-CPR (ECMO) compared with C-CPR
<table>
<tr><th>Outcome</th><th>E-CPR (ECMO)
n (%)</th><th>C-CPR
n (%)</th><th>P value</th></tr>
<tr><td colspan="4">All (cardiogenic and non-cardiogenic); N = 60 in E-ECP and 60 in C-CPR</td></tr>
<tr><td>In-hospital survival</td><td>19 (31.7)</td><td>6 (10.0)</td><td>0.011</td></tr>
<tr><td>6-month survival</td><td>16 (26.7)</td><td>5 (8.3)</td><td>0.019</td></tr>
<tr><td>1-year survival</td><td>13 (21.6)</td><td>5 (8.3)</td><td>0.004</td></tr>
<tr><td>2-year survival</td><td>12 (20.0)</td><td>5 (8.3)</td><td>0.005</td></tr>
<tr><td>At discharge, CPC score ≤ 2</td><td>14 (23.3)</td><td>3 (5.0)</td><td>0.013</td></tr>
<tr><td>6-month, CPC score ≤ 2</td><td>14 (23.3)</td><td>3 (5.0)</td><td>0.013</td></tr>
<tr><td colspan="4">Subgroup (cardiogenic); N = 45 in E-ECP and 45 in C-CPR</td></tr>
<tr><td>In-hospital survival</td><td>16 (35.5)</td><td>4 (8.8)</td><td>0.004</td></tr>
<tr><td>6-month survival</td><td>13 (28.9)</td><td>4 (8.9)</td><td>0.035</td></tr>
<tr><td>At discharge, CPC score ≤ 2</td><td>12 (26.7)</td><td>4 (8.8)</td><td>0.035</td></tr>
<tr><td>6-month, CPC score ≤ 2</td><td>12 (26.7)</td><td>4 (6.7)</td><td>0.035</td></tr>
</table>
Survival with minimal neurologic impairment for E-CPR (ECMO) versus C-CPR from multivariate analysis
<table>
<tr><th>Outcome</th><th>Effect measure
OR (95% CI) or HR (95% CI)</th></tr>
<tr><td colspan="2">All (cardiogenic and non-cardiogenic)</td></tr>
<tr><td>In-hospital survival, OR (95% CI)</td><td>0.17 (0.04 to 0.71)[a]</td></tr>
<tr><td>6-month survival, HR (95% CI)</td><td>0.50 (0.30 to 0.84)[a]</td></tr>
<tr><td>1-year survival, HR (95% CI)</td><td>0.55 (0.37 to 0.83)</td></tr>
<tr><td>2-year survival, HR (95% CI)</td><td>0.56 (0.37 to 0.84)</td></tr>
<tr><td colspan="2">Subgroup (cardiogenic)</td></tr>
<tr><td>In-hospital survival, OR (95% CI)</td><td>0.19 (0.04 to 0.88)[a]</td></tr>
<tr><td>6-month survival, HR (95% CI)</td><td>0.60 (0.34 to 1.05)[a]</td></tr>
<tr><td colspan="2">[a]Adjusted with propensity score</td></tr>
</table>
Authors' Conclusion:
"E-CPR showed a benefit with regard to neurologically intact survival over C-CPR after the propensity score-matching process for patients who received CPR for > 10 mins after an in hospital witnessed arrest, especially in case of cardiac origin." P.6
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Lin,[18] 2010, Taiwan</td><td>
Main Findings:
Outcomes with E-CPR (ECMO) compared with C-CPR in adult patients
<table>
<tr><th>Outcome</th><th>E-CPR (ECMO)
N = 27</th><th>C-CPR
N = 27</th><th>P value</th></tr>
<tr><td>Survival, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>to discharge</td><td>8 (29.6)</td><td>5 (18.5)</td><td>NR</td></tr>
<tr><td>to 1 month</td><td>9 (33.3)</td><td>7 (25.9)</td><td>0.551</td></tr>
<tr><td>to 6 months</td><td>8 (29.6)</td><td>4 (14.8)</td><td>0.327</td></tr>
<tr><td>to 1 year</td><td>6 (22.2)</td><td>3 (11.1)</td><td>0.467</td></tr>
<tr><td colspan="4">Neurological status assessed by CPC status, n</td></tr>
<tr><td>CPC at discharge: (1 or 2) and (3 or 4)</td><td>7 and 1</td><td>5 and 0</td><td>0.460</td></tr>
<tr><td>CPC at 1 year: (1 or 2) and (3 or 4)</td><td>5 and 1</td><td>3 and 0</td><td>0.427</td></tr>
</table>
Hazard ratio (HR) from survival curves for E-CPR compared with C-CPR
<table>
<tr><td>Time period</td><td>HR (95% CI)</td><td>P value</td></tr>
<tr><td>Up to 30 days</td><td>0.86 (0.45 to 1.62)</td><td>0.634</td></tr>
<tr><td>Up to 6 months</td><td>0.59 (0.32 to 1.08)</td><td>0.09</td></tr>
<tr><td>Up to 1 year</td><td>0.60 (0.33 to 1.09)</td><td>0.09</td></tr>
</table>
Authors' Conclusion:
"This study failed to demonstrate a survival difference between patients who had ROSB after institution of ECMO and those who had ROSC after conventional CPR. Further studies evaluating the role of ECMO in conventional CPR rescued patients are warranted." P. 796

(CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; ROSB = return of spontaneous beating; ROSC = return of spontaneous circulation)
</td></tr>
<tr><td>Chen,[19] 2008, Taiwan</td><td>
Main Findings:
Outcomes with E-CPR (ECMO) compared with C-CP in adult patients
<table>
<tr><th>Outcome</th><th>E-CPR (ECMO)
N = 46</th><th>C-CPR
N = 46</th><th>P value</th></tr>
<tr><td colspan="4">Neurological status assessed by CPC status at discharge, n (%)</td></tr>
<tr><td>CPC: 1 or 2</td><td>14 (30.4)</td><td>7 (15.2)</td><td>0.09</td></tr>
<tr><td>CPC: 3 or 4</td><td>1 (2.2)</td><td>1 (2.2)</td><td>0.09</td></tr>
<tr><td>CPC: 5 (death)</td><td>31 (67.4)</td><td>38 (82.6)</td><td>0.09</td></tr>
<tr><td colspan="4">Neurological status assessed by CPC status at 1 year, n (%)</td></tr>
<tr><td>CPC: 1 or 2</td><td>9 (19.5)</td><td>5 (10.8)</td><td>0.27</td></tr>
<tr><td>CPC: 3 or 4</td><td>1 (2.2)</td><td>1 (2.2)</td><td>0.27</td></tr>
<tr><td>CPC: 5 (death)</td><td>36 (78.3)</td><td>40 (87.0)</td><td>0.27</td></tr>
</table>
Hazard ratio (HR) from survival curves for E-CPR compared with C-CPR
<table>
<tr><td>Time period</td><td>HR (95% CI)</td><td>P value</td></tr>
<tr><td>Up to 30 days</td><td>0.47 (0.28 to 0.77)</td><td>0.003</td></tr>
<tr><td>Up to 1 year</td><td>0.53 (0.33 to 0.83)</td><td>0.006</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>Authors' Conclusion:
"Extracorporeal CPR had a short-term and long-term survival benefit over conventional CPR in patients with in-hospital cardiac arrest of cardiac origin." P. 554

(CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; ROSB = return of spontaneous beating; ROSC = return of spontaneous circulation)</td></tr>
<tr><td colspan="2">ECMO versus VAD</td></tr>
<tr><td colspan="2">Systematic review</td></tr>
<tr><td>Urban,[15] 2013, Czech Republic</td><td>Main Findings:
Outcomes with ECMO compared with VAD from retrospective observational studies
<table>
<tr><th rowspan="2">Study, country</th><th rowspan="2">Patient group</th><th colspan="3">Survival (%)</th></tr>
<tr><th>ECMO</th><th>VAD</th><th>P value</th></tr>
<tr><td>Taghavi, Austria</td><td>13 ECMO (2000 to 2003)
15 RVAD (1984 to 2000)</td><td>54</td><td>33 (RVAD)</td><td>0.274</td></tr>
<tr><td>D'Alessandro et al., France</td><td>54 ECMO (2000 to 2006)
6 RVAD (2000 to 2003)
2 BiVAD (2000 to 2003)</td><td>50[a]</td><td>33 (RVAD)[a]
0 (BiVAD)[a]</td><td>NR</td></tr>
<tr><td>Mihajlevic et al., USA</td><td>43 ECMO (1990 to 2009)
6 RVAD (1900 to 2009)
4 BiVAD (1990 to 2009)</td><td colspan="2">1-month survival: 43,
1-year survival: 40
Type of device did not appear to affect survival</td><td>NR</td></tr>
<tr><td colspan="5">[a] survival at discharge</td></tr>
</table>
Authors' Conclusion:
"We conclude that there is insufficient evidence to prefer ECMO over VAD and the optimal modality of mechanical circulatory support (MCS) following heart transplantation should be determined by the surgeon and institutional experience and dependent on the extent and severity of myocardial dysfunction and the presence or absence of associated respiratory insufficiency." P. 517</td></tr>
<tr><td colspan="2">Non randomized study</td></tr>
<tr><td>Fraser,[20] 2012, USA</td><td>Main Findings:
<table>
<tr><th rowspan="2">Outcome[a]</th><th colspan="3">Cohort 1</th><th colspan="3">Cohort 2</th></tr>
<tr><th>ECMO N = 48</th><th>VAD N = 24</th><th>P value</th><th>ECMO N = 48</th><th>VAD N = 24</th><th>P value</th></tr>
<tr><td colspan="7">Outcome at 30 days; n or n (%)</td></tr>
<tr><td>Received transplant</td><td>NA</td><td>11</td><td>NR</td><td>NA</td><td>5</td><td>NR</td></tr>
<tr><td>Weaned with recovery</td><td>36[b]</td><td>0</td><td>NR</td><td>32[b]</td><td>1</td><td>NR</td></tr>
<tr><td>Weaned with poor outcome[c]</td><td>2</td><td>0</td><td>NR</td><td>6</td><td>0</td><td>NR</td></tr>
<tr><td>Died</td><td>10</td><td>1</td><td>NR</td><td>10</td><td>1</td><td>NR</td></tr>
<tr><td>Success[d]</td><td>36 (75)</td><td>23 (96)</td><td>0.048</td><td>32 (67)</td><td>23 (96)</td><td>0.007</td></tr>
<tr><td colspan="7">Outcome at end of circulatory support; n or n (%)</td></tr>
</table></td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

Received transplant	NA	21	NR	NA	21	NR
Weaned with recovery	3 [b]	0	NR	32 [b]	1	NR
Weaned with poor outcome [b]	2	1	NR	6	0	NR
Died	10	2	NR	10	2	NR
Success [e]	36 (75)	21 (88)	0.059	32 (67)	22 (92)	0.021

[a] "The days by which no participants were still alive and receiving circulatory support were as follows: 174 days in cohort 1, 21 days in the ECMO group for cohort 1, 192 days in cohort 2, and 28 days in the ECMO group for cohort 2." P. 539

[b] "Data from patients who underwent device explantation and survived for at least 30 days were censored; the ELSO database does not specify whether such explants are due to recovery or transplantation." P.539

[c] A poor outcome in the ventricular-assist group was defined as death or an unacceptable neurologic outcome within 30 days after weaning or before discharge from the hospital, whichever was longer. A poor outcome in the ECMO group was defined as death within 30 days after weaning from the device; data on neurologic outcomes were unavailable from the ELSO database. P.539

[d] "Success at 30 days in the ventricular-assist group was defined as being alive and receiving circulatory support with the device, having undergone transplantation, or having been weaned from the device with an acceptable neurologic outcome within 30 days after device removal. Success at 30 days in the ECMO group was defined as being alive and receiving circulatory support with ECMO or having been successfully weaned from ECMO, either owing to transplantation or weaning without death within 30 days after device removal." P.539

[e] "Success at the end of device support in the ventricular-assist group was defined as having undergone transplantation or having been weaned from the device with an acceptable neurologic outcome within 30 days after device removal. Success at the end of device support in the ECMO group was defined as weaning from ECMO because of transplantation or recovery" p. 539.

Authors' Conclusion:

"In conclusion, we found that a ventricular assist device available in several sizes for use in children as a bridge to heart transplantation was associated with a significantly higher rate of survival, as compared with ECMO. Serious adverse events, including infection, stroke, and bleeding, occurred in a majority of the study participants." P. 540

C-CPR = conventional cardiopulmonary resuscitation; CI = confidence interval; CPC = cerebral performance category; ECMO = extracorporeal membrane oxygenation; E-CPR = extracorporeal cardiopulmonary resuscitation; ELSO = Extracorporeal Life Support Organization; LOS = length of hospital stay; E-CPR = extracorporeal cardiopulmonary resuscitation; HR = hazard ratio; NA = not available; NR = not reported; OR = odds ratio;

APPENDIX 5: Guidelines and Recommendations

Guideline Society, Country, Author, Year	Recommendations
NICE guidance,[21] 2014	"The evidence on the efficacy of extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults is adequate but there is uncertainty about which patients are likely to benefit from this procedure, and the evidence on safety shows a high incidence of serious complications. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. Clinicians wishing to undertake ECMO for acute heart failure in adults should take the following actions. • Inform the clinical governance leads in their NHS trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Submit data on all adults undergoing ECMO for acute heart failure to the International Extracorporeal Life Support Organizational register. ECMO for acute heart failure in adults should only be carried out by clinical teams with specific training and expertise in the procedure." P.2